

Amendments to the Specification:

Please replace the paragraph beginning at page 19, line 17 and ending on page 19, line 27, with the following rewritten paragraph:

-- For example, an enzymatic assay to determine the activity of a ~~histone deacetylase~~ HDAC inhibitor compound can be conducted as follows. Briefly, the effect of an HDAC inhibitor compound on affinity purified human epitope-tagged (Flag) HDAC1 can be assayed by incubating the enzyme preparation in the absence of substrate on ice for about 20 minutes with the indicated amount of inhibitor compound. Substrate ($[^3\text{H}]$ acetyl-labelled murine erythroleukemia cell-derived histone) can be added and the sample can be incubated for 20 minutes at 37°C in a total volume of 30 μL . The reaction can then be stopped and released acetate can be extracted and the amount of radioactivity release determined by scintillation counting. An alternative assay useful for determining the activity of a ~~histone deacetylase~~ HDAC inhibitor compound is the "HDAC Fluorescent Activity Assay; Drug Discovery Kit-AK-500" available from BIOMOL® Research Laboratories, Inc., Plymouth Meeting, PA. --

Please replace the section beginning at page 20, line 16 and ending on page 20, line 22, with the following rewritten section:

-- Thus, the present invention includes within its broad scope compositions comprising HDAC inhibitors which are 1) hydroxamic acid derivatives; 2) Short-Chain Fatty Acids (SCFAs); 3) cyclic tetrapeptides; 4) benzamides; 5) electrophilic ketones; and/or any other class of compounds capable of inhibiting histone deacetylases, for use in inhibiting histone deacetylase, inducing terminal differentiation, cell growth arrest and/or apoptosis in neoplastic cells, and /or inducing differentiation, cell growth arrest and/or apoptosis of tumor cells in a tumor.

~~Examples~~ Non-limiting examples of such HDAC inhibitors ~~include, but are not limited to:~~ are set forth below. It is understood that the present invention includes any salts, crystal structures, amorphous structures, hydrates, derivatives, metabolites, stereoisomers, structural isomers and prodrugs of the HDAC inhibitors described herein.

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Please replace the section beginning at page 20, line 23 and ending on page 45, line 2, with the following rewritten section:

-- A. **Hydroxamic Acid Derivatives** such as suberoylanilide hydroxamic acid (SAHA) (Richon *et al.*, Proc. Natl. Acad. Sci. USA 95,3003-3007 (1998)); m-carboxycinnamic acid bishydroxamide (CBHA) (Richon *et al.*, supra); pyroxamide; trichostatin analogues such as trichostatin A (TSA) and trichostatin C (Koghe *et al.* 1998. Biochem. Pharmacol. 56: 1359-1364); ~~salicylylhydroxamic acid~~ salicylhydroxamic acid (SBHA) (Andrews *et al.*, International J. Parasitology 30,761-768 (2000)); suberoyl bishydroxamic acid (SBHA) (U.S. Patent No. 5,608,108); azelaic bishydroxamic acid (ABHA) (Andrews *et al.*, supra); azelaic-1-hydroxamate-9-anilide (AAHA) (Qiu *et al.*, Mol. Biol. Cell 11, 2069-2083 (2000)); 6-(3-chlorophenylureido) carpoic hydroxamic acid (3Cl-UCHA); oxamflatin [(2E)-5-[3-[(phenylsulfonyl) aminol phenyl]-pent-2-en-4-ynohydroxamic acid] (Kim *et al.* Oncogene, 18: 2461 2470 (1999)); A-161906, Scriptaid (Su *et al.* 2000 Cancer Research, 60: 3137-3142); PXD-101 (Prolifix); LAQ-824; CHAP; MW2796 (Andrews *et al.*, supra); MW2996 (Andrews *et al.*, supra); or any of the hydroxamic acids disclosed in U.S. Patent Numbers 5,369,108, 5,932,616, 5,700,811, 6,087,367 and 6,511, 990.

B. **Cyclic Tetrapeptides** such as trapoxin A (TPX)-cyclic tetrapeptide (cyclo-(L-phenylalanyl-L-phenylalanyl-D-pipecolinyl-L-2-amino-8-oxo-9,10-epoxy decanoyl)) (Kijima *et al.*, J Biol. Chem. 268,22429-22435 (1993)); FR901228 (FK 228, depsipeptide) (Nakajima *et al.*, Ex. Cell Res. 241,126-133 (1998)); FR225497 cyclic tetrapeptide (H. Mori *et al.*, PCT Application WO 00/08048 (17 February 2000)); apicidin cyclic tetrapeptide [cyclo(N-O-methyl-L-tryptophanyl-L -isoleucinyl-D-pipecolinyl-L-2-amino-8-oxodecanoyl)] (Darkin-Rattray *et al.*, Proc. Natl. Acad. Sci. USA 93,1314313147 (1996)); apicidin Ia, apicidin Ib, apicidin Ic, apicidin IIa, and apicidin IIb (P. Dulski *et al.*, PCT Application WO 97/11366); CHAP, HC-toxin cyclic tetrapeptide (Bosch *et al.*, Plant Cell 7, 1941-1950 (1995)); WF27082 cyclic tetrapeptide (PCT Application WO 98/48825); and chlamydocin (Bosch *et al.*, supra).

C. **Short chain fatty acid (SCFA) derivatives** such as: sodium butyrate (Cousens *et al.*, J. Biol. Chem. 254,1716-1723 (1979)); isovalerate (McBain *et al.*, Biochem. Pharm. 53: 1357-1368 (1997)); valerate (McBain *et al.*, supra) ; 4-

phenylbutyrate (4-PBA) (Lea and Tulsyan, Anticancer Research, 15,879-873 (1995)); phenylbutyrate (PB) (Wang *et al.*, Cancer Research, 59, 2766-2799 (1999)); propionate (McBain *et al.*, supra); butyramide (Lea and Tulsyan, supra); isobutyramide (Lea and Tulsyan, supra); phenylacetate (Lea and Tulsyan, supra); 3-bromopropionate (Lea and Tulsyan, supra); tributyrin (Guan *et al.*, Cancer Research, 60,749-755 (2000)); valproic acid and valproate and PivanexTM.

D. **Benzamide derivatives** such as CI-994; MS-27-275 [N- (2-aminophenyl)-4- [N-(pyridin-3-yl methoxycarbonyl) aminomethyl] benzamide] (Saito *et al.*, Proc. Natl. Acad. Sci. USA 96, 4592-4597 (1999)); and 3'-amino derivative of MS-27-275 (Saito *et al.*, supra).

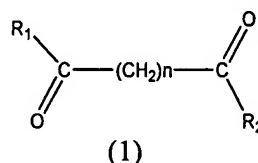
E. **Electrophilic ketone derivatives** such as trifluoromethyl ketones (Frey *et al.*, Bioorganic & Med. Chem. Lett. (2002), 12, 3443-3447; U.S. 6,511,990) and α -keto amides such as N-methyl- α -ketoamides

F. **Other HDAC Inhibitors** such as ~~depudecin~~ depudecin, psammaplins and depudecin (Kwon *et al.* 1998. PNAS 95: 3356-3361, 3361).

Preferred hydroxamic acid based HDAC inhibitors are suberoylanilide hydroxamic acid (SAHA), m-carboxycinnamic acid bishydroxamate (CBHA) and pyroxamide. SAHA has been shown to bind directly in the catalytic pocket of the histone deacetylase enzyme. SAHA induces cell cycle arrest, differentiation and/or apoptosis of transformed cells in culture and inhibits tumor growth in rodents. SAHA is effective at inducing these effects in both solid tumors and hematological cancers. It has been shown that SAHA is effective at inhibiting tumor growth in animals with no toxicity to the animal. The SAHA-induced inhibition of tumor growth is associated with an accumulation of acetylated histones in the tumor. SAHA is effective at inhibiting the development and continued growth of carcinogen-induced (N-methylnitrosourea) mammary tumors in rats. SAHA was administered to the rats in their diet over the 130 days of the study. Thus, SAHA is a nontoxic, orally active antitumor agent whose mechanism of action involves the inhibition of histone deacetylase activity.

Preferred HDAC inhibitors are those disclosed in U.S. Patent Numbers 5,369,108, 5,932,616, 5,700,811, 6,087,367 and 6,511, 990, issued to some of the present inventors disclose compounds, the entire contents of which are incorporated herein by reference, non-limiting examples of which are set forth below:

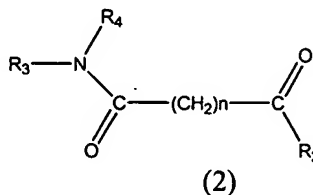
~~Thus, in~~ In one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound is~~ represented by the structure of formula 1, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



wherein R₁ and R₂ can be the same or different; when R₁ and R₂ are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine or thiazoleamino group; when R₁ and R₂ are different R₁=R₃-N-R₄, wherein each of R₃ and R₄ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl alkyloxy, aryloxy, arylalkyloxy or pyridine group, or R₃ and R₄ are bonded together to form a piperidine group, R₂ is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group and n is an integer from about 4 to about 8.

In a particular embodiment of ~~Formula~~ formula 1, R₁ and R₂ are the same and are a substituted or unsubstituted thiazoleamino group; and n is an integer from about 4 to about 8.

~~In another one~~ In one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound is~~ represented by the structure of formula 2, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



wherein each of R₃ and R₄ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or

unbranched alkyl, alkenyl, cycloalkyl, arylalkyloxy, aryloxy, arylalkyloxy or pyridine group, or R₃ and R₄ are bonded together to form a piperidine group, R₂ is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group and n is an integer from about 4 to about 8.

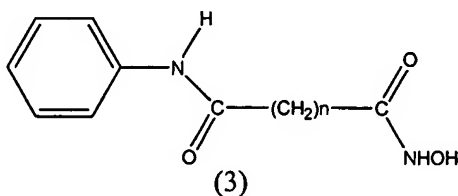
In a particular embodiment of formula 2, each of R₃ and R₄ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R₃ and R₄ bond together to form a piperidine group; R₂ is a hydroxylamino, hydroxyl, amino, alkylamino, or alkyloxy group; n is an integer from 5 to 7; and R₃-N-R₄ and R₂ are different.

In another particular embodiment of ~~Formula~~formula 2, n is 6. In yet another embodiment of ~~Formula~~formula H₂, R₄ is a hydrogen atom, R₃ is a substituted or unsubstituted phenyl and n is 6. In yet another embodiment of ~~Formula~~formula H₂, R₄ is a hydrogen atom, R₃ is a substituted phenyl and n is 6, wherein the phenyl substituent is selected from the group consisting of a methyl, cyano, nitro, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylamino carbonyl, or hydroxylaminocarbonyl group.

In another embodiment of formula 2, n is 6, R₄ is a hydrogen atom and R₃ is a cyclohexyl group. In another embodiment of formula 2, n is 6, R₄ is a hydrogen atom and R₃ is a methoxy group. In another embodiment of formula 2, n is 6 and R₃ and R₄ bond together to form a piperidine group. In another embodiment of formula 2, n is 6, R₄ is a hydrogen atom and R₃ is a benzyloxy group. In another embodiment of formula 2, R₄ is a hydrogen atom and R₃ is a γ -pyridine group. In another embodiment of formula 2, R₄ is a hydrogen atom and R₃ is a β -pyridine group. In another embodiment of formula 2, R₄ is a hydrogen atom and R₃ is an α -pyridine group. In another embodiment of formula 2, n is 6, and R₃ and R₄ are both methyl groups. In another embodiment of formula ~~H₂~~2, n is 6, R₄ is a methyl group and R₃ is a phenyl group.

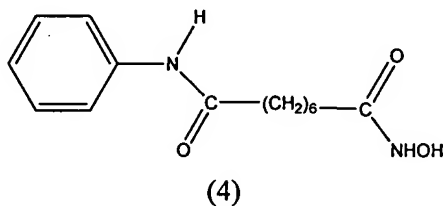
In ~~another~~one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~is

represented by the structure of formula 3, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.:~~

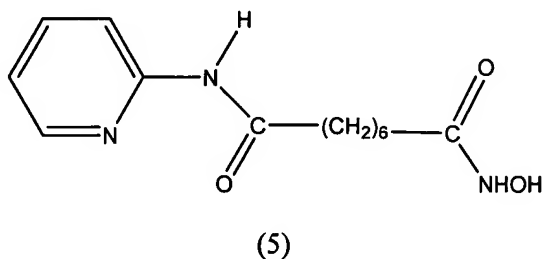


wherein n is an integer from 5 to about 8.

In a preferred embodiment of formula 3, n is 6. In accordance with this embodiment, the ~~present invention provides a pharmaceutical composition comprising~~ HDAC inhibitor is SAHA (4), or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.:~~ SAHA can be represented by the following structural formula:

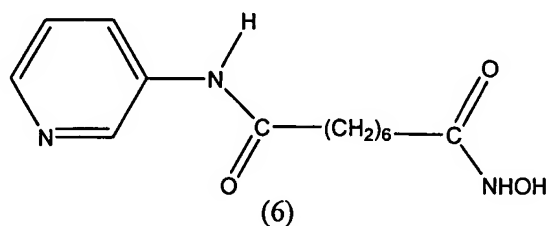


In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the ~~present invention provides a pharmaceutical composition comprising a compound is~~ represented by the structure of formula 5, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.:~~

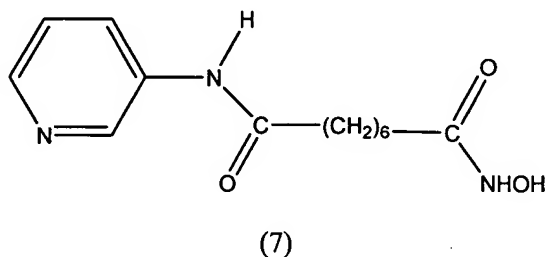


In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the ~~present invention provides a pharmaceutical composition comprising a compound is~~

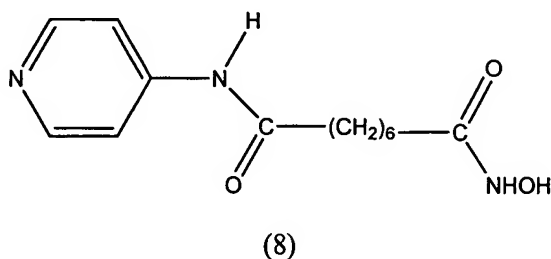
represented by the structure of formula 6 (pyroxamide), or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



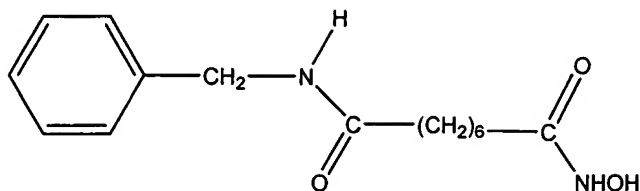
In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 7, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 8, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~

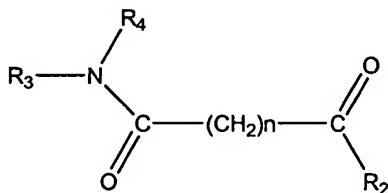


In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 9, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



(9)

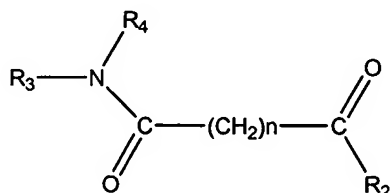
In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 10, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



(10)

wherein R₃ is hydrogen and R₄ cycloalkyl, aryl, aryloxy, arylalkyloxy, or pyridine group, or R₃ and R₄ bond together to form a piperidine group; R₂ is a hydroxylamino group; and n is an integer from 5 to about 8.

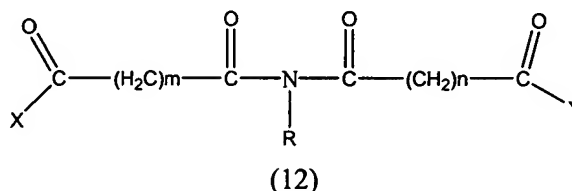
In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 11, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



(11)

wherein R₃ and R₄ are independently a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, cycloalkyl, aryl, aryloxy, arylalkyloxy, or pyridine group, or R₃ and R₄ bond together to form a piperidine group; R₂ is a hydroxylamino group; and n is an integer from 5 to about 8.

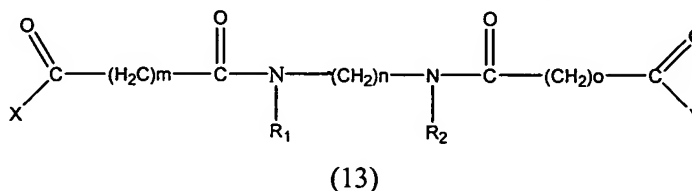
In ~~another~~one embodiment, the HDAC inhibitor useful in the methods of the
present invention ~~provides a pharmaceutical composition comprising a compound~~is
represented by the structure of formula 12, or a pharmaceutically acceptable salt or
hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.:~~



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; R is a hydrogen atom, a hydroxyl, group, a substituted or unsubstituted alkyl, arylalkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In a particular embodiment, the HDAC inhibitor is a compound of **Formula XI2** wherein X, Y and R are each hydroxyl and both m and n are 5.

In ~~another~~one embodiment, the HDAC inhibitor useful in the methods of the
present invention ~~provides a pharmaceutical composition comprising a compound~~is
~~represented by the structure of formula 13, or a pharmaceutically acceptable salt or~~
~~hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:~~

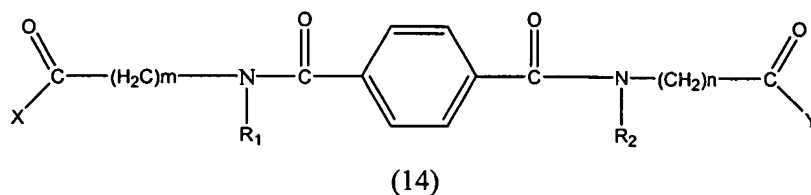


wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkoxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkoxyamino, aryloxyamino, alkoxyalkylamino or aryloxyalkylamino group; each of R₁ and R₂ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkoxy, or aryloxy group; and each of m, n and

o are independently the same as or different from each other and are each an integer from about 0 to about 8.

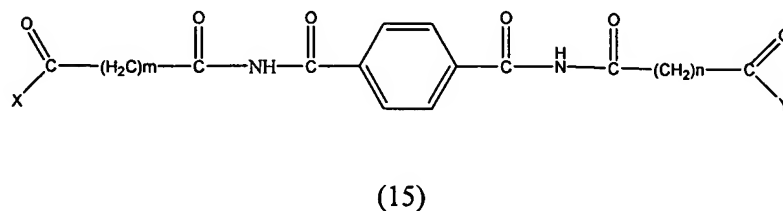
In one particular embodiment of formula 13, each of X and Y is a hydroxyl group and each of R₁ and R₂ is a methyl group. In another particular embodiment of formula 13, each of X and Y is a hydroxyl group, each of R₁ and R₂ is a methyl group, each of n and o is 6, and m is 2.

In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 14, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; each of R₁ and R₂ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 15, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~

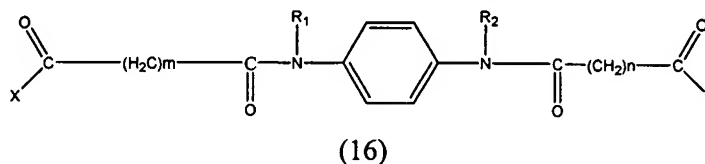


wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or

unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

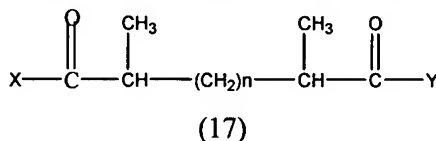
In one particular embodiment of formula ~~15~~15, each of X and Y is a hydroxyl group and each of m and n is 5.

In ~~another~~one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~is represented by the structure of formula 16, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; R₁ and R₂ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, arylalkyloxy or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

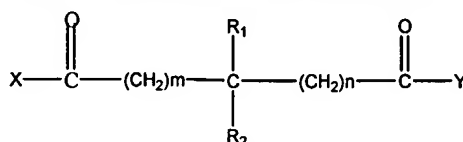
In ~~another~~one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~is represented by the structure of formula 17, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, or aryloxyalkylamino group; and n is an integer from about 0 to about 8.

In one particular embodiment of formula 17, each of X and Y is a hydroxylamino group; R₁ is a methyl group, R₂ is a hydrogen atom; and each of m and n is 2. In another particular embodiment of formula 17, each of X and Y is a hydroxylamino group; R₁ is a carbonylhydroxylamino group, R₂ is a hydrogen atom; and each of m and n is 5. In another particular embodiment of formula 17, each of X and Y is a hydroxylamino group; each of R₁ and R₂ is a fluoro group; and each of m and n is 2.

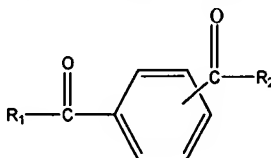
In ~~another one~~ embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound is~~ represented by the structure of formula 18, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



(18)

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; each of R₁ and R₂ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, aryloxy, carbonylhydroxylamino or fluoro group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In ~~another one~~ embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound is~~ represented by the structure of formula 19, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~

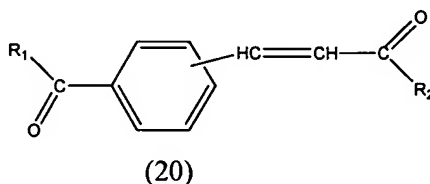


(19)

wherein each of R₁ and R₂ are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group. In a particular embodiment, the HDAC inhibitor is a compound of structural ~~Formula~~formula XIX wherein R₁ and R₂ are both hydroxylamino.

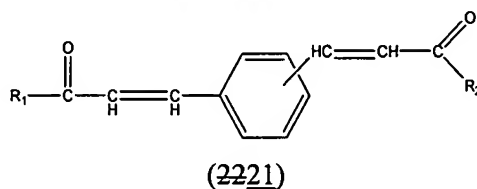
In one particular embodiment of formula 19, R₁ is a phenylamino group and R₂ is a hydroxylamino group.

~~In another one~~ In another embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 20, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



wherein each of R₁ and R₂ are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group. In a particular embodiment, the HDAC inhibitor is a compound of structural ~~Formula~~formula XXI wherein R₁ and R₂ are both hydroxylamino.

~~In one particular embodiment of formula XVIII, R₁ is a hydroxylamino group. In another particular embodiment of formula 21, R₂ is a hydroxylamino group. In another embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula ~~22, 21~~, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~

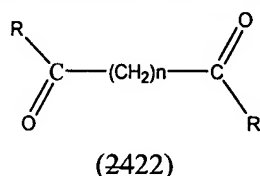


wherein each of R₁ and R₂ are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino,

alkylaryl amino, alkyl oxy amino, aryl oxy amino, alkyl oxy alkyl amino, or aryl oxy alkyl amino group. In a particular embodiment, the HDAC inhibitor is a compound of structural ~~Formula~~ formula 2421 wherein R₁ and R₂ are both hydroxyl amino-

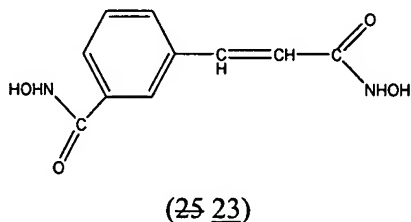
~~In one particular embodiment of formula 23, R₁ is a phenyl amino group and R₂ is a hydroxyl amino group.~~

~~In another embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 24,22, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.;~~



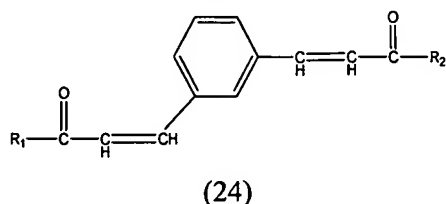
wherein R is a phenyl amino group substituted with a cyano, methylcyano, nitro, carboxyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, trifluoromethyl, hydroxylaminocarbonyl, N-hydroxylaminocarbonyl, methoxycarbonyl, chloro, fluoro, methyl, methoxy, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 2,6-difluoro, 3,5-difluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 1,2,3-trifluoro, 3,4,5-trifluoro, 2,3,4,5-tetrafluoro, or 2,3,4,5,6-pentafluoro group; and n is an integer from 4 to 8.

~~In another embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 2523 (m-carboxycinnamic acid bishydroxamide - CBHA), or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.;~~

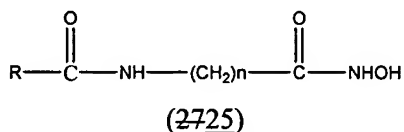


~~In another embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is~~

represented by the structure of formula ~~26~~24, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



In ~~another~~one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~is represented by the structure of formula ~~27~~25, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



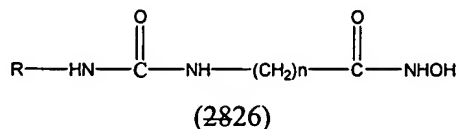
wherein R is a substituted or unsubstituted phenyl, piperidine, thiazole, 2-pyridine, 3-pyridine or 4-pyridine and n is an integer from about 4 to about 8.

In one particular embodiment of formula ~~27~~25, R is a substituted phenyl group. In another particular embodiment of formula ~~27~~25, R is a substituted phenyl group, where the substituent is selected from the group consisting of methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenyloxy, benzyloxy, phenylaminoxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

In another particular embodiment of formula ~~27~~25, R is a substituted or unsubstituted 2-pyridine, 3-pyridine or 4-pyridine and n is an integer from about 4 to about 8.

In ~~another~~one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~is

represented by the structure of formula ~~28,26~~, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~

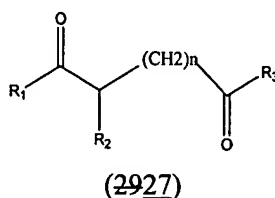


wherein R is a substituted or unsubstituted phenyl, pyridine, piperidine or thiazole group and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

In a particular embodiment of formula ~~28,26~~, R is a substituted phenyl group. In another particular embodiment of formula ~~28,26~~, R is a substituted phenyl group, where the substituent is selected from the group consisting of methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methyloxy, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, methyloxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

In another particular embodiment of formula ~~28,26~~, R is phenyl and n is 5. In another embodiment, n is 5 and R is 3-chlorophenyl.

~~In another one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is~~ represented by the structure of formula ~~29,27~~, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~

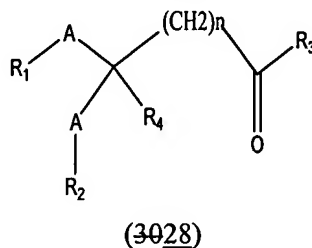


wherein each of R₁ and R₂ is directly attached or through a linker and is substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, or

quinolinyl or isoquinolinyl; n is an integer from about 3 to about 10 and R₃ is a hydroxamic acid, hydroxylamino, hydroxyl, amino, alkylamino or alkyloxy group. The linker can be an amide moiety, e.g., O-, -S-, -NH-, NR₅, -CH₂-, -(CH₂)_m-, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof, wherein R₅ is a substitute or unsubstituted C₁-C₅ alkyl.

In certain embodiments of formula ~~29,27~~, R₁ is -NH-R₄ wherein R₄ is substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl.

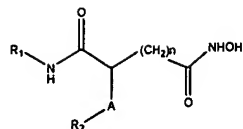
In ~~another~~ one embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula ~~30,28~~, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~



wherein each of R₁ and R₂ is, substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; R₃ is hydroxamic acid, hydroxylamino, hydroxyl, amino, alkylamino or alkyloxy group; R₄ is hydrogen, halogen, phenyl or a cycloalkyl moiety; and A can be the same or different and represents an amide moiety, O-, -S-, -NH-, NR₅, -CH₂-, -(CH₂)_m-, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof wherein R₅ is a substitute or unsubstituted C₁-C₅ alkyl; and n and m are each an integer from 3 to 10.

In further particular embodiment a compounds having a more specific structure within the scope of compounds ~~2927~~ or ~~3028~~ are compound 29.

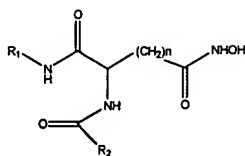
~~A compound~~ In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula ~~31-29~~, or a pharmaceutically acceptable salt or hydrate thereof:



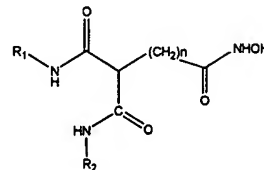
(3129)

wherein A is an amide moiety, R₁ and R₂ are each selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; and n is an integer from 3 to 10.

For example, the compound of formula ~~3029~~ can have the structure ~~3130~~ or ~~3231~~:



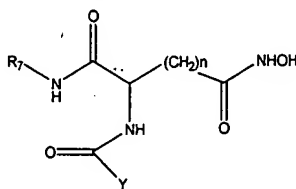
(3130)



(3231)

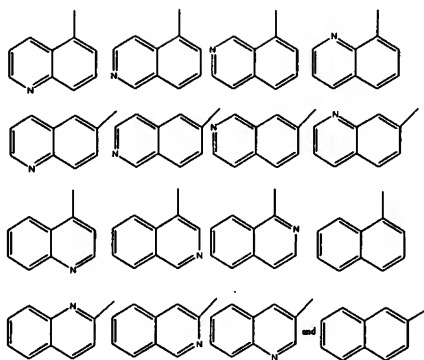
wherein R₁, R₂ and n have the meanings of ~~Formula~~formula 30-29.

~~A compound~~In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 3332 or a pharmaceutically acceptable salt or hydrate thereof:

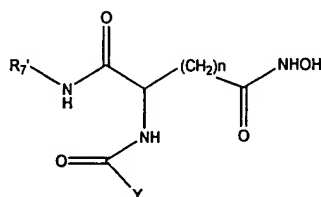


(3332)

wherein R₇ is selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; n is an integer from 3 to 10 and Y is selected from:

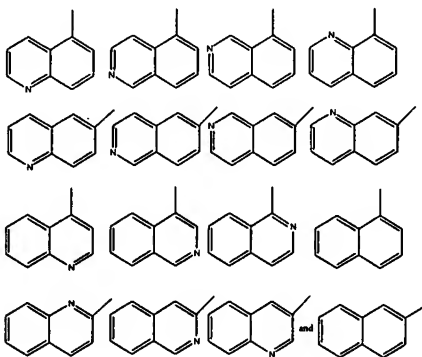


A compoundIn one embodiment, the HDAC inhibitor useful in the methods of
the present invention is represented by the structure of formula 3433 or a
pharmaceutically acceptable salt or hydrate thereof:

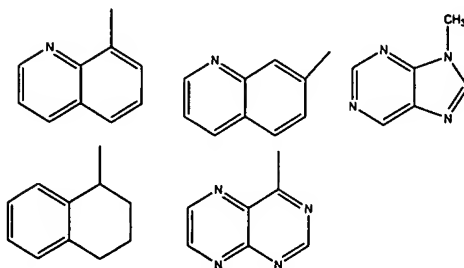


(3433)

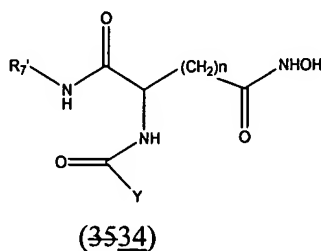
wherein n is an integer from 3 to 10, Y is selected from



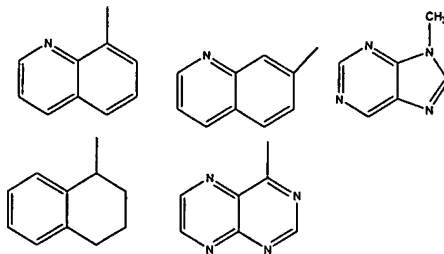
and R7' is selected from



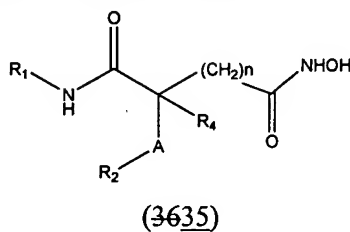
~~A compound~~In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula ~~3534~~ or a pharmaceutically acceptable salt or hydrate thereof:



aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinoliny or isoquinoliny; n is an integer from 3 to 10 and R₇' is selected from

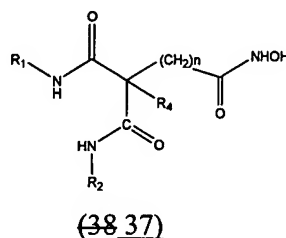
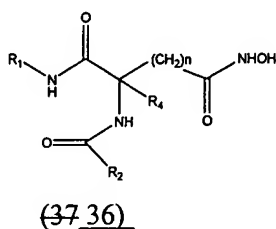


~~A compound~~In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula ~~3635~~ or a pharmaceutically acceptable salt or hydrate thereof:



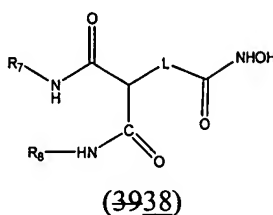
wherein A is an amide moiety, R₁ and R₂ are each selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinoliny or isoquinoliny; R₄ is hydrogen, a halogen, a phenyl or a cycloalkyl moiety and n is an integer from 3 to 10.

For example, the compound of formula ~~36~~35 can have the structure of formulas 36 or 37-or-38:



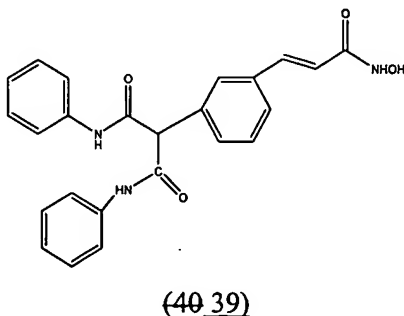
wherein R₁, R₂, R₄ and n have the meanings of ~~Formula~~formula 36-35.

~~A compound~~In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 39~~38~~ or a pharmaceutically acceptable salt or hydrate thereof:



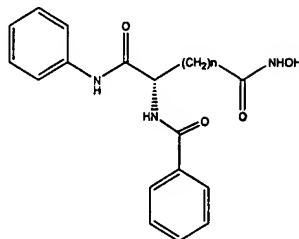
wherein L is a linker selected from the group consisting of an amide moiety, O-, -S-, -NH-, NR₅, -CH₂-, -(CH₂)_m-, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof wherein R₅ is a substitute or unsubstituted C₁-C₅ alkyl; and wherein each of R₇ and R₈ are independently a substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinoliny or isoquinoliny; n is an integer from 3 to 10 and m is an integer from 0-10.

For example, a compound of ~~Formula~~formula 39~~38~~ can be represented by the structure of formula (39):



Other HDAC inhibitors suitable for use in the methods of the present invention include those shown in the following more specific formulas:

A compound represented by the structure:

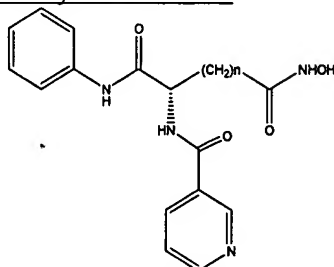


(41 40)

wherein n is an integer from 3 to 10, or an enantiomer thereof. In one particular embodiment of formula 40, n=5.

~~Other HDAC inhibitors suitable for use in the invention include those shown in the following more specific formulas:~~

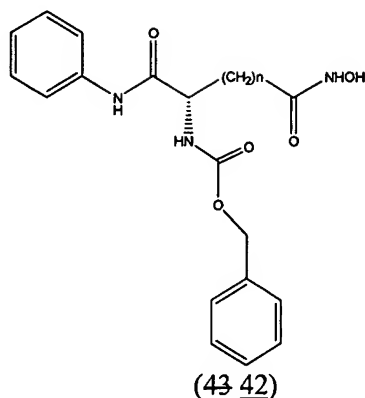
A compound represented by the structure:



(42 41)

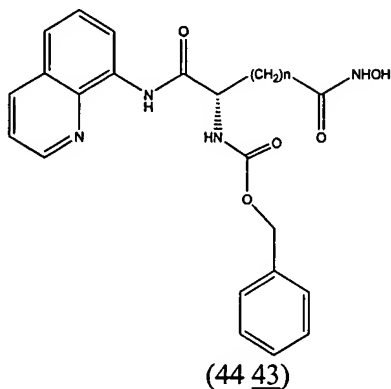
~~wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 42 41, n=5.~~

A compound represented by the structure:



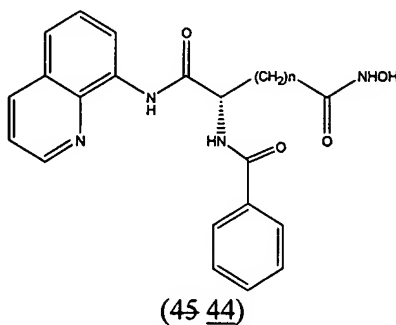
wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula ~~43~~ 42, n=5.

A compound represented by the structure:



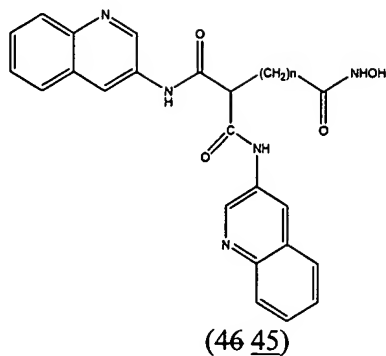
wherein n is an integer from 3 to 10, or an enantiomer thereof. In one particular embodiment of formula ~~44~~ 43, n=5.

A compound represented by the structure:



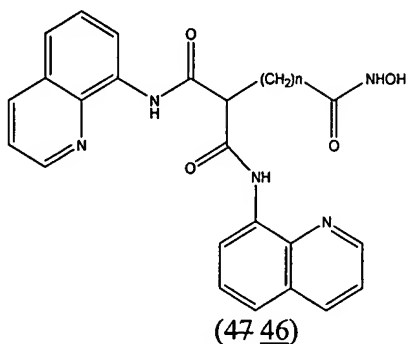
wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula ~~45~~ 44, n=5.

A compound represented by the structure:



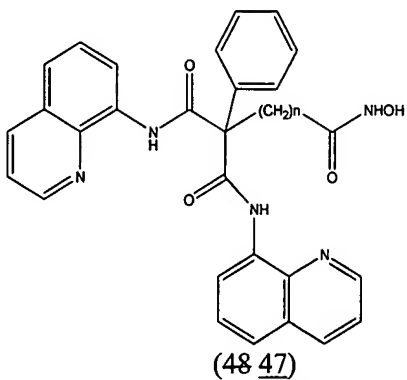
wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 46 45, n=5.

A compound represented by the structure:



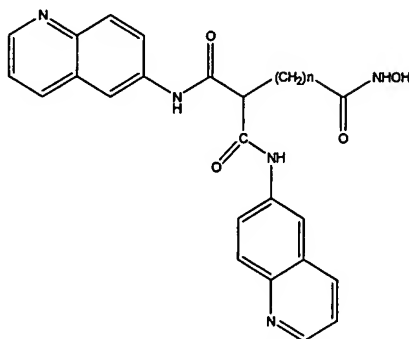
wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 47 46, n=5.

A compound represented by the structure:



wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 48 47, n=5.

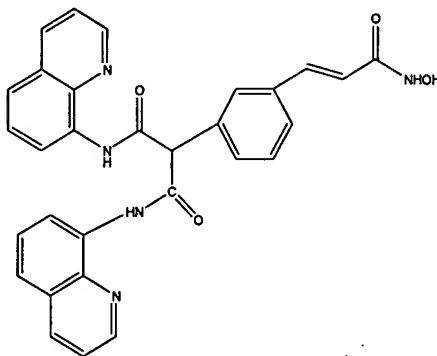
A compound represented by the structure:



(49 48)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 49 48, n=5.

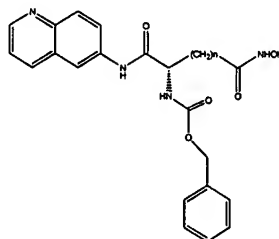
A compound represented by the structure:



(50 49)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 50 49, n=5.

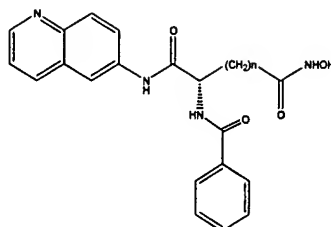
A compound represented by the structure:



(51 50)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula ~~51~~ 50, n=5.

A compound represented by the structure:



(~~52~~ 51)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula ~~52~~ 51, n=5. --

Please replace the following section beginning at page 46, line 10, ending at page 46, line 18, with the following rewritten section:

-- The invention also encompasses pharmaceutical compositions comprising hydrates of the HDAC inhibitors and/or the anti-cancer agents. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like.

~~This~~In addition, this invention also encompasses pharmaceutical compositions comprising any solid or liquid physical form of SAHA or any of the other HDAC inhibitors. For example, The HDAC inhibitors can be in a crystalline form, in amorphous form, and have any particle size. The HDAC inhibitor particles may be micronized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical form. --

Please replace the paragraph beginning at page 53, line 8, ending on page 53, line 14, with the following rewritten paragraph:

-- II. Syndromes combining progressive dementia with other prominent neurologic abnormalities such as A) syndromes appearing mainly in adults (e.g., Huntington's disease, Multiple system atrophy combining dementia with ataxia ~~and/or manifestations~~

and/or manifestations of Parkinson's disease, Progressive supranuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy body disease, and corticodentatonigral degeneration); and B) syndromes appearing mainly in children or young adults (e.g., Hallervorden-Spatz disease and progressive familial myoclonic epilepsy). --

Please replace the paragraph beginning at page 61, line 14, ending on page 61, line 23, with the following rewritten paragraph:

-- Figures 1 to 8 are HPLC slides showing the amount of α -ACh4 in patients in Cohorts I and II, measured at up to 10 hours after receiving the oral dose, compared with the α -ACh4 levels when SAHA was administered intravenously. Fig 9 shows the mean plasma concentration of SAHA (ng/ml) at the indicated time points following administration. Fig 9A: Oral dose (200 mg and 400 mg) under fasting on Day 8. Fig 9B: Oral dose (200 mg and 400 mg) with food on Day 9. Fig 9C: IV dose on day 1. Fig 10 shows the apparent half-life of a SAHA 200 mg and 400 mg oral dose, on Days 8, 9 and 22. Fig 11 shows the AUC (ng/ml/hr) of a SAHA 200 mg and 400 mg oral dose, on Days 8, 9 and 22. Figure 12 shows the bioavailability of SAHA after a 200 mg and 400 mg oral dose, on Days 8, 9 and 22. --

Please replace the title of Example 3 at page 62, line 1, with the following rewritten title:

-- Oral dosing of suberoylanilide ~~hydroxyamic~~hydroxamic acid (SAHA) -- Dose Escalation. --